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(54) Title: A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF OBESITY OR TO FACILITATE OR PROMOTE WEIGHT LOSS

(57) Abstract: Pharmaceutical compositions are disclosed for the treatment of obesity, an overweight condition and compulsive overeating. The pharmaceutical compositions are comprised of a therapeutically effective combination of a nicotinic receptor partial agonist and a CB-1 receptor antagonist and a pharmaceutically acceptable carrier. The method of using these compounds is also disclosed.

A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF OBESITY OR TO FACILITATE OR PROMOTE WEIGHT LOSS

Background of the Invention

The present invention relates to pharmaceutical compositions for the treatment of obesity, compulsive overeating; or to facilitate or promote weight loss in a mammal (e.g. human) comprising a nicotinic receptor partial agonist (NRPA) and a CB-1 receptor antagonist. The term NRPA refers to all chemical compounds that bind at neuronal nicotinic acetylcholine specific receptor sites in mammalian tissue and elicit a partial agonist response. A partial agonist response is defined here to mean a partial, or incomplete functional effect in a given functional assay. Additionally, a partial agonist will also exhibit some degree of antagonist activity by its ability to block the action of a full agonist (Feldman, R.S., Meyer, J.S. & Quenzer, L.F. Principles of Neuropsychopharmacology, 1997; Sinauer Assoc. Inc.). As used herein, the term "CB-1 Antagonists" refers to both full antagonists and partial antagonists, as well as inverse agonists of the G-protein coupled type 1 cannabinoid receptor. For a review of cannabinoid CB1 and CB2 receptor modulators, see Pertwee, R.G., "Cannabinoid Receptor Ligands: Clinical and Neuropharmacological Considerations, Relevant to Future Drug Discovery and Development," Exp. Opin. Invest. Drugs, 9(7), 1553-1571 (2000). The present invention may be used to treat mammals (e.g. humans) for obesity, an overweight condition or compulsive overeating with a decrease in the severity of unwanted side effects such as causing nausea and/or stomach upset.

Obesity is a major health risk that leads to increased mortality and incidence of Type 2 diabetes mellitus, hypertension and dyslipidemia. It is the second leading cause of preventable death in the United States, and contributes to >300,000 deaths per year. The estimated direct annual health cost associated with obesity is $70 billion, while the total overall cost to the U.S. economy has been estimated to be over $140 billion. In the U.S., more than 50% of the adult population is overweight, and almost ¼ of the population is considered to be obese (BMI greater than or equal to 30). Furthermore, the prevalence of obesity in the United States has increased by about 50% in the past 10 years. While the vast majority of obesity occurs in the industrialized world, particularly in US and Europe, the prevalence of obesity is also increasing in Japan. The prevalence of obesity in adults is 10%-25% in most countries of Western Europe. The rise in the incidence of obesity has promoted the WHO to recognize obesity as a significant disease. What is needed are orally active agents that induce sustained weight loss of 10-15% of initial body weight, due to selective loss of body fat in moderately obese patients. These orally active agents should increase energy expenditure, decrease food intake and partition energy away from adipose tissue. This degree of sustained weight loss would then improve comorbidities including hyperglycemia, hypertension and hyperlipidemia, all of which are exacerbated by obesity.

However, even though weight loss agents have therapeutic utility in the treatment of obesity, there are significant liabilities to the use of weight loss compounds. Specifically, many of these compounds that have been tested in humans can cause potentially serious side effects such as gastrointestinal complications including nausea, emesis, ulcers, constipation, flatulence, diarrhea, hypertension, respiratory depression, and psychological and physical dependence.

Summary of Invention

The present invention relates to a pharmaceutical composition for the treatment of obesity, compulsive overeating and/or to promote or facilitate weight loss comprising

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof;

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier;

wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating obesity, compulsive overeating and/or facilitating or promoting weight loss.

In a more specific embodiment of the invention the suitable CB-1 receptor antagonists include: (1) purine compounds such as those described in U.S. Provisional Application No. 60/421874, filed on October 28, 2002 and incorporated herein by reference; (2) pyrazolo[1,5-a][1,3,5]triazine compounds such as those described in U.S. Provisional Application No. 60/445728, filed on February 6, 2003 and incorporated herein by reference; (3) pyrazolo[1,5-a]pyrimidine compounds such as those described in U.S. Provisional Application No. 60/446450, filed on February 10, 2003 and incorporated herein by reference; (4) 1,4- and 2,4-disubstituted imidazoles such as those disclosed in U.S. Provisional Application No. 60/419621, filed on October 18, 2002 and incorporated herein by reference; (5) 1-(1,5-diaryl-1H-pyrazol-3-yl)-2-(substituted amino)-ethanone compounds such as those described in U.S. Provisional Application No. 60/432911, filed on December 12, 2002 and incorporated herein by reference; (6) 1-(1,5-diaryl-1H-pyrazol-3-yl)-2-(substituted amino)-ethanol compounds such as those described in U.S. Provisional Application No. 60/432911, filed on December 12, 2002 and incorporated herein by reference; (7) 2-(1,5-diaryl-1H-pyrazol-3-yl)morpholine compounds such as those described in U.S. Provisional Application No. 60/432911, filed on December 12, 2002 and incorporated herein by reference; and (8) 1-(1,2-diaryl-1H-imidazol-4-yl)-2-(substituted amino)-ethanone compounds such as those described in U.S. Provisional Application No. 60/432911, filed on December 12, 2002 and incorporated herein by reference;

CB-1 receptor antagonist purine compounds are selected from: 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-ethylamino-azetidine-3-carboxylic acid amide; 1-

[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 1-{1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-phenylpiperidin-4-yl}-ethanone; {3-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-3-(1α,5α,6α)-azabicyclo[3.1.0]hex-6-yl}-dimethylamine; 6-(1-benzylpyrrolidin-3-yloxy)-9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purine; 9-(4-chlorophenyl)-6-(1-cyclohexylazetidin-3-yloxy)-8-(2,4-dichlorophenyl)-9H-purine; 6-tert-butoxy-9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purine; 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-isopropoxy-9H-purine; 1-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-2-methyl-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-pyrrolidin-1-yl-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 4-amino-1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-4-methylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 8-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 9-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-methyl-4-oxa-1,9-diazaspiro[5.5]undecan-2-one; 8-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-phenylpiperidin-4-ol; 4-benzyl-1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidin-4-ol; 4-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperazine-2-carboxylic acid methylamide; 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-9H-purine; and 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-(4-pyrimidin-2-yl-piperazin-1-yl)-9H-purine; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-isopropylamino-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-isopropylamino-piperidine-4-carboxylic acid amide; 4-amino-1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic acid amide; 8-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 4-amino-1-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidine-4-carboxylic acid amide; and 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylaminopiperidine-4-

carboxylic acid amide; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

CB-1 receptor antagonist pyrazolo[1,5-a}[1,3,5]triazine compounds are selected from: 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-methylpiperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-pyrimidin-2-ylpiperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-[(1S,4S)-5-methanesulfonyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylpyrazolo[1,5-a][1,3,5]triazine; and 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-[4-(propane-2-sulfonyl)-piperazin-1-yl]-pyrazolo[1,5-a][1,3,5]triazine; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-methylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-fluorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 3-amino-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-azetidine-3-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-methylaminoazetidine-3-carboxylic acid amide; and 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-dimethylaminoazetidine-3-carboxylic acid amide; 1-{1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-phenylpiperidin-4-yl}-ethanone; 3-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-azabicyclo[3.1.0]hex-6-ylamine; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 4-benzyl-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-piperidin-4-ol; 2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-5-methyl-2,5,7-triazaspiro[3.4]octan-8-one; 2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5,7-triazaspiro[3.4]octan-8-one; 8-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-6,6-dimethyl-2,5,7-triazaspiro[3.4]octan-8-one; 4-(1-benzylpyrrolidin-3-yloxy)-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-(1-cyclohexylazetidin-3-yloxy)-2-methylpyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxy-2-methylpyrazolo[1,5-a][1,3,5]triazine; and 4-tert-butoxy-7-(2-

chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine; butyl-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-amine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-piperidin-1-yl-pyrazolo[1,5-a][1,3,5]triazine; [7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-[2-(4-fluorophenyl)-ethyl]-amine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-morpholin-4-yl-pyrazolo[1,5-a][1,3,5]triazine; and [7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-(2-morpholin-4-yl-ethyl)-amine; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 3-amino-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-azetidine-3-carboxylic acid amide; and 8-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

CB-1 receptor antagonist pyrazolo[1,5-a]pyrimidine compounds are selected from: 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-(4-methyl-piperazin-1-yl)-pyrazolo[1,5-a]pyrimidine; 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrazolo[1,5-a]pyrimidine; 3-(4-chloro-phenyl)-2-(2-chlorophenyl)-7-[(1S,4S)-5-methanesulfonyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-pyrazolo[1,5-a]pyrimidine; and 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-[4-(propane-2-sulfonyl)-piperazin-1-yl]-pyrazolo[1,5-a]pyrimidine; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 3-amino-1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-azetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-6-methylpyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylamino-azetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-methylaminoazetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-{1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-phenylpiperidin-4-yl}-ethanone; 3-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-(1a,5a,6a)-azabicyclo[3.1.0]hex-6-ylamine; 1-[3-(4-chlorophenyl)-2-(2-

chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 4-benzyl-1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-piperidin-4-ol; 8-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 2-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-2,5,7-triazaspiro[3.4]octan-8-one; 8-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-6-methylpyrazolo[1,5-a]pyrimidin-7-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 2-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-5-methyl-2,5,7-triazaspiro[3.4]octan-8-one; 7-(1-benzylpyrrolidin-3-yloxy)-3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidine; and 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-(1-cyclohexylazetidin-3-yloxy)-pyrazolo[1,5-a]pyrimidine; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; and 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 8-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

CB-1 receptor antagonist 1,4- and 2,4-disubstituted imidazoles are selected from: 5-(4-chloro-phenyl)-3-(5-cyclohexyl-1H-imidazol-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole; 5-(4-chloro-phenyl)-3-(2-cyclohexyl-3H-imidazol-4-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-3-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-3-[1-(1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-3-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-3-[1-(2,2-dimethyl-tetrahydro-pyran-4-yl)-1H-imidazol-4-yl]-4-methyl-1H-pyrazole: 5-{2-(2,4-dichloro-phenyl)-4-methyl-5-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-2H-pyrazol-3-yl}-2-methoxy-pyridine; and 1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-3-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of the compound or the salt.

CB-1 receptor antagonist 1-(1,5-diaryl-1H-pyrazol-3-yl)-2-(substituted amino)-ethanone compounds are selected from: 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-1H-pyrrole-2-carbonyl)-piperazin-1-yl]-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-cyclopropanecarbonyl)-piperazin-1-yl]-ethanone; N-(1-{2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2,2,2-trifluoro-acetamide;

1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoroacetyl-piperazin-1-yl)-ethanone; 1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-pyrrolidin-1-yl-ethanone; 1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[1,4]oxazepan-4-yl-ethanone; and 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-oxa-8-aza-spiro[4.5]dec-8-yl)-ethanone; and a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound or the salt.

CB-1 receptor antagonist 1-(1,5-diaryl-1H-pyrazol-3-yl)-2-(substituted amino)-ethanol compounds are selected from: 2-(benzyl-isopropyl-amino)-1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,5-dimethyl-piperidin-1-yl)-ethanol; 1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanol; and 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanol; and a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound or the salt.

CB-1 receptor antagonist 2-(1,5-diaryl-1H-pyrazol-3-yl)morpholine compounds are selected from: 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-cyclohexyl-morpholine; 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(propane-2-sulfonyl)-morpholine; 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(toluene-4-sulfonyl)-morpholine; 1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-yl}-2-methyl-propan-1-one; and 2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(4-trifluoromethyl-benzyl)-morpholine; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of the compound or the salt.

CB-1 receptor antagonist 1-(1,2-diaryl-1H-imidazol-4-yl)-2-(substituted amino)-ethanone compounds are selected from: 1-(1,2-diaryl-1H-imidazol-4-yl)-2-(substituted amino)-ethanone compounds include: 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-piperidin-1-yl-ethanone and 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone; and a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound, or the salt.

In another more specific embodiment of this invention, the nicotinic receptor partial agonist is selected from:

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)- 1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,6-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

5-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

7-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

6-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

4,5-difluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-6-ol;

6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;

4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and

6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene and

their pharmaceutically acceptable salts and their optical isomers.

Preferably, the nicotinic receptor partial agonist is selected from:

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;

1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;

11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;

1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;

4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and

11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol and

their pharmaceutically acceptable salts and their optical isomers.

The present invention also relates to a method of treating obesity, overeating, and/or facilitating or promoting weight loss in a mammal comprising administering to said mammal

respectively an anti-obesity attenuating effective amount of a pharmaceutical composition comprising

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof; and

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof;

wherein the active ingredients (a) and (b) are present in amounts that render the composition effective in the treatment of obesity, compulsive overeating or an overweight condition.

In another more specific embodiment of this invention the nicotinic receptor partial agonist is selected from:

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)- 1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;

1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;
7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;
4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;
6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,6-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;
7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
4,5-difluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-6-ol;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;

4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and
6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene and
their pharmaceutically acceptable salts and their optical isomers.

Preferably, the nicotinic receptor partial agonist is selected from:
9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;
4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;
6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;
5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;
10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;
1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;
11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;
1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;
4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;
5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;
6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;
5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;
6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;
6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and
11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;

and the pharmaceutically acceptable salts stereoisomers (including optical isomers), solvates and hydrates of the foregoing compounds.

In another more specific embodiment, the anti-obesity agent and/or weight loss promoter or facilitator is described herein above and includes its pharmaceutically acceptable salts, hydrates and solvates.

The invention also relates to pharmaceutical composition for treating a disorder or condition selected from the group consisting of disorders and conditions in which obesity or an overweight condition predominates, including Type 2 diabetes mellitus, hypertension, dyslipidemia, and increased mortality in a mammal, including a human, comprising administering to said mammal;

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof,

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof;

(c) a pharmaceutically acceptable carrier;

wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating obesity or an overweight condition predominates, including Type 2 diabetes mellitus, hypertension, dyslipidemia and increased mortality in a mammal, including a human comprising;.

The invention also relates to a method of treating a disorder or condition selected from the group of disorders and conditions in which obesity or an overweight condition predominates, including Type 2 diabetes mellitus, hypertension, dyslipidemia, and increased mortality in a mammal, including a human, comprising administering to said mammal;

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof; and

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof;

wherein the active ingredients (a) and (b) above are present in amounts that render the combination of the two active agents effective in treating such disorder or condition.

The nicotinic receptor partial agonist and the CB-1 receptor antagonist can be administered substantially simultaneously.

The term "treating" as used herein, refers to reversing, alleviating, inhibiting or slowing the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

Detailed Description of the Invention

In combination with the NRPA, the invention includes a CB-1 receptor antagonist.

A nicotine partial agonist combined with a CB-1 receptor antagonist may facilitate weight loss while reducing the incidence of undesirable side effects. Nicotine has long been appreciated to have anorectic properties, but its use has been limited by a poor spectrum of activity, side effects, and less efficacy than anti-obesity agents. This may be due to lack of specificity of nicotine for neuromuscular, ganglionic, and central nervous system receptors. The development of nicotine partial agonists with specific receptor subtype affinities is an approach to potentially reduce side effects and enhance efficacy. (see Li, Ming D. et al., "Nicotine, Body Weight and Potential Implications in the Treatment of Obesity", Current Topics in Medicinal Chemistry, 2003, 3, 899-919).

Over the past several years it has become clear that obesity has an important genetic component. Scientific investigation of monogenic rodent models of obesity has revealed novel mechanisms important in the regulation of body weight homeostasis including leptin or a leptin receptor. Several of these genes are now the targets of drug discovery efforts. Human obesity, however, is rarely due to monogenic causes but rather is a result of complex multigenic and environmental interactions. Despite the important role of genetics in the predisposition to obesity in humans, the obese phenotype results only after prolonged positive energy balance due to excess energy consumption or insufficient energy expenditure. Conversely, weight loss can only take place when energy expenditure exceeds energy intake over an extended interval. Weight loss can be achieved by stimulating energy expenditure, decreasing caloric intake, decreasing energy absorption and/or favorable partitioning of energy to skeletal muscle where it is converted to muscle mass as opposed to adipose tissue where it is stored. The goal is to achieve sustained weight loss of 5-15% or greater leading to an improvement of glycemic control up to a 2% decrease in HbA1c in diabetics, reductions in diastolic blood pressure to 90 mm Hg in hypertensives, and/or decreases in LDL cholesterol by ≥ 15% in hyperlipidemic patients. CB-1 receptor antagonists have been shown to treat obesity by inducing weight loss in human clinical trials.

The particular NRPA compounds listed above, which can be employed in the methods and pharmaceutical compositions of this invention, can be made by processes known in the chemical arts, for example by the methods described in WO 9818798 A1 (US Patent

6,235,734), WO 9935131-A1 (US Patent 6,410,550) and WO9955680-A1 (US Patent 6,462,035). Some of the preparation methods useful for making the compounds of this invention may require protection of remote functionality (i.e., primary amine, secondary amine, carboxyl). The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily determined by one skilled in the art, and is described in examples carefully described in the above cited applications. The starting materials and reagents for the NRPA compounds employed in this invention are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. Some of the compounds used herein are related to, or are derived from compounds found in nature and accordingly many such compounds are commercially available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature.

Some of the NRPA compounds employed in this invention are ionizable at physiological conditions. Thus, for example some of the compounds of this invention are acidic and they form a salt with a pharmaceutically acceptable cation. The use of all such salts are within the scope of the pharmaceutical compositions and methods this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the acidic and basic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

In addition, some of the NRPA compounds employed in this invention are basic, and form a salt with a pharmaceutically acceptable acid. All such salts are within the scope of this invention and they can be prepared by conventional methods. For example, they can be prepared simply by contacting the basic and acidic entities, usually in a stoichiometric ratio, in either an aqueous, non-aqueous or partially aqueous medium, as appropriate. The salts are recovered either by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by lyophilization, as appropriate.

The utility of the NRPA compounds employed in the present invention as medicinal agents in the treatment of obesity, compulsive overeating, and an overweight condition in mammals (e.g. humans) is demonstrated by the activity of the compounds of this invention in conventional assays and, in particular the assays described below. Such assays also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these

comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

Procedures

Receptor binding assay: The effectiveness of the active compounds in suppressing nicotine binding to specific receptor sites is determined by the following procedure which is a modification of the methods of Lippiello, P. M. and Fernandes, K. G. (in The Binding of L-[^{3}H]Nicotine To A Single Class of High-Affinity Sites in Rat Brain Membranes, Molecular Pharm., 29, 448-54, (1986)) and Anderson, D. J. and Arneric, S. P. (in Nicotinic Receptor Binding of ^{3}H-Cystisine, ^{3}H-Nicotine and ^{3}H-Methylcarmbamylcholine In Rat Brain, European J. Pharm., 253, 261-67 (1994)). Male Sprague-Dawley rats (200-300 g) from Charles River were housed in groups in hanging stainless steel wire cages and were maintained on a 12 hour light/dark cycle (7 a.m.-7 p.m. light period). They received standard Purina Rat Chow and water *ad libitum*. The rats were killed by decapitation. Brains were removed immediately following decapitation. Membranes were prepared from brain tissue according to the methods of Lippiello and Fernandez (Molec Pharmacol, 29, 448-454, (1986) with some modifications. Whole brains were removed, rinsed with ice-cold buffer, and homogenized at 0 °C in 10 volumes of buffer (w/v) using a Brinkmann Polytron™, setting 6, for 30 seconds. The buffer consisted of 50 mM Tris HCl at a pH of 7.5 at room temperature. The homogenate was sedimented by centrifugation (10 minutes; 50,000 x g; 0 to 4 °C). The supernatant was poured off and the membranes were gently resuspended with the Polytron and centrifuged again (10 minutes; 50,000 x g; 0 to 4 °C. After the second centrifugation, the membranes were resuspended in assay buffer at a concentration of 1.0 g/100 mL. The composition of the standard assay buffer was 50 mM Tris HCl, 120 mM NaCl, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$ and has a pH of 7.4 at room temperature.

Routine assays were performed in borosilicate glass test tubes. The assay mixture typically consisted of 0.9 mg of membrane protein in a final incubation volume of 1.0 mL. Three sets of tubes were prepared wherein the tubes in each set contained 50 µL of vehicle, blank, or test compound solution, respectively. To each tube was added 200 µL of [^{3}H]-nicotine in assay buffer followed by 750 µL of the membrane suspension. The final concentration of nicotine in each tube was 0.9 nM. The final concentration of cytisine in the blank was 1 µM. The vehicle consisted of deionized water containing 30 µL of 1 N acetic acid per 50 mL of water. The test compounds and cytisine were dissolved in vehicle. Assays were initiated by vortexing after addition of the membrane suspension to the tube. The samples were incubated at 0 to 4 °C in an iced shaking water bath. Incubations were terminated by rapid filtration under vacuum through Whatman GF/B™ glass fiber filters using a Brandel™ multi-manifold tissue harvester. Following the initial filtration of the assay mixture, filters were washed two times with ice-cold assay buffer (5 m each). The filters were then placed in counting vials and mixed vigorously with 20 ml of

Ready Safe™ (Beckman) before quantification of radioactivity. Samples were counted in a LKB Wallach Rackbeta™ liquid scintillation counter at 40-50% efficiency. All determinations were in triplicate.

Calculations: Specific binding (C) to the membrane is the difference between total binding in the samples containing vehicle only and membrane (A) and non-specific binding in the samples containing the membrane and cytisine (B), i.e.,

Specific binding = (C) = (A) - (B).

Specific binding in the presence of the test compound (E) is the difference between the total binding in the presence of the test compound (D) and non-specific binding (B), i.e., (E) = (D) - (B).

% Inhibition = (1-((E)/(C)) times 100.

The compounds of the invention that were tested in the above assay exhibited IC_{50} values of less than 10μM.

Dopamine Turnover:

Rats were injected s.c. or p.o. (gavage) and then decapitated either 1 or 2 hours later. Nucleus accumbens was rapidly dissected (2 mm slices, 4 °C, in 0.32 M sucrose), placed in 0.1 N perchloric acid, and then homogenized. After centrifugation 10 uL of the supernatant was assayed by HPLC-ECD. Turnover/ utilization of dopamine (DA) was calculated as the ratio of tissue concentrations of metabolites ([DOPAC]+[HVA]) to DA and expressed as percent of control.

PHARMACOLOGICAL TESTING PF CB-1 RECEPTOR ANTAGONIST

The utility of the compounds of the present invention in the practice of the instant invention can be evidenced by activity in at least one of the protocols described hereinbelow. The following acronyms are used in the protocols described below.

BSA - bovine serum albumin

DMSO - dimethylsulfoxide

EDTA - ethylenediamine tetracetic acid

PBS -- phosphate-buffered saline

EGTA - ethylene glycol-*bis*(β-aminoethyl ether) N,N,N',N'-tetraacetic acid

GDP - guanosine diphosphate

sc - subcutaneous

po - orally

ip - intraperitoneal

icv - intra cerebro ventricular

iv - intravenous

[^{3}H]SR141716A - radiolabeled N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride available from Amersham Biosciences, Piscataway, NJ.

[^{3}H]CP-55940 - radiolabled 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol available from NEN Life Science Products, Boston, MA.

AM251 - *N* -(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide available from Tocris™, Ellisville, MO.

In Vitro Biological Assays

Bioassay systems for determining the CB-1 and CB-2 binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor Ligands" Current Medicinal Chemistry, 6, 635-664 (1999) and in WO 92/02640 (U.S. Application No. 07/564,075 filed August 8, 1990, incorporated herein by reference).

The following assays were designed to detect compounds that inhibit the binding of [^{3}H] SR141716A (selective radiolabeled CB-1 ligand) and [^{3}H] 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol ([^{3}H] CP-55940; radiolabeled CB-1/CB-2 ligand) to their respective receptors.

Rat CB-1 Receptor Binding Protocol

PelFreeze brains (available from Pel Freeze Biologicals, Rogers, Arkansas) were cut up and placed in tissue preparation buffer (5 mM Tris HCl, pH = 7.4 and 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000 X g for 5 minutes at 4 °C. The supernatant was recovered and centrifuged at 100,000 X G for 1 hour at 4 °C. The pellet was then re-suspended in 25 ml of TME (25 nM Tris, pH = 7.4, 5 mM $MgCl_2$, and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. A BCA protein assay was used to determine the appropriate tissue concentration and then 200 µl of rat brain tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 20 °C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

Human CB-1 Receptor Binding Protocol

Human embryonic kidney 293 (HEK 293) cells transfected with the CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in homogenization buffer (10 mM EDTA, 10 mM EGTA, 10 mM Na Bicarbonate, protease inhibitors; pH = 7.4), and homogenized with a Dounce Homogenizer. The homogenate was then spun at 1,000X g for 5 minutes at 4 °C. The supernatant was recovered and centrifuged at 25,000X G for 20 minutes at 4 °C. The pellet was then re-suspended in 10 ml of homogenization buffer and re-spun at 25,000X G for 20 minutes at 4 °C. The final pellet was re-suspended in 1ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA). A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [3H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. The plates were covered and placed in an incubator at 30 °C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

CB-2 Receptor Binding Protocol

Chinese hamster ovary-K1 (CHO-K1) cells transfected with CB-2 cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in tissue preparation buffer (5 mM Tris-HCl buffer (pH = 7.4) containing 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000X g for 5 minutes at 4 °C. The supernatant was recovered and centrifuged at 100,000X G for 1 hour at 4 °C. The pellet was then re-suspended in 25 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 10 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO, and 80.5% TME) and then 25 µl were added to the deep well polypropylene plate. [3H] CP-55940 was diluted a ligand buffer (0.5% BSA and 99.5% TME) and then 25 µl were added to each well at a concentration of 1 nM. A BCA protein assay was used to determine the appropriate tissue concentration and 200 µl of the tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 30 °C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the

reaction plate. The plates were then harvested by Skatron format onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. The filters were then counted on the Wallac Betaplate™ counter.

CB-1 GTPγ [^{35}S] Binding Assay

Membranes were prepared from CHO-K1 cells stably transfected with the human CB-1 receptor cDNA. Membranes were prepared from cells as described by Bass et al, in "Identification and characterization of novel somatostatin antagonists," Molecular Pharmacology, 50, 709-715 (1996). GTPγ [^{35}S] binding assays were performed in a 96 well FlashPlate™ format in duplicate using 100 pM GTPγ[^{35}S] and 10 μg membrane per well in assay buffer composed of 50 mM Tris HCl, pH 7.4, 3 mM $MgCl_2$, pH 7.4, 10 mM $MgCl_2$, 20 mM EGTA, 100 mM NaCl, 30 μM GDP, 0.1 % bovine serum albumin and the following protease inhibitors: 100 μg/ml bacitracin, 100 μg/ml benzamidine, 5 μg/ml aprotinin, 5 μg/ml leupeptin. The assay mix was then incubated with increasing concentrations of antagonist (10^{-10} M to 10^{-5} M) for 10 minutes and challenged with the cannabinoid agonist CP-55940 (10 μM). Assays were performed at 30 °C for one hour. The FlashPlates™ were then centrifuged at 2000Xg for 10 minutes. Stimulation of GTPγ[^{35}S] binding was then quantified using a Wallac Microbeta.EC_{50} calculations done using Prism™ by Graphpad.

Inverse agonism was measured in the absense of agonist.

CB-1 FLIPR-based Functional Assay Protocol

CHO-K1 cells co-transfected with the human CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) and the promiscuous G-protein G16 were used for this assay. Cells were plated 48 hours in advance at 12500 cells per well on collagen coated 384 well black clear assay plates. Cells were incubated for one hour with 4μM Fluo-4 AM (Molecular Probes) in DMEM (Gibco) containing 2.5 mM probenicid and pluronic acid (.04%). The plates were then washed 3 times with HEPES-buffered saline (containing probenicid; 2.5 mM) to remove excess dye. After 20 min the plates were added to the FLIPR individually and fluorescence levels was continuously monitored over an 80 s period. Compound additions were made simultaneously to all 384 wells after 20 s of baseline. Assays were performed in triplicate and 6 point concentration-response curves generated. Antagonist compounds were subsequently challenged with 3μM WIN 55,212-2 (agonist). Data were analyzed using Graph Pad Prism.

Detection of Inverse Agonists

The following cyclic-AMP assay protocol using intact cells was used to determine inverse agonist activity.

Cells were plated into a 96-well plate at a plating density of 10,000-14,000 cells per well at a concentration of 100 μl per well. The plates were incubated for 24 hours in a 37 °C

incubator. The media was removed and media lacking serum (100 µl) was added. The plates were then incubated for 18 hours at 37 °C.

Serum free medium containing 1 mM IBMX was added to each well followed by 10 µl of test compound (1:10 stock solution (25 mM compound in DMSO) into 50% DMSO/PBS) diluted 10X in PBS with 0.1% BSA. After incubating for 20 minutes at 37°C, 2 µM of Forskolin was added and then incubated for an additional 20 minutes at 37 °C. The media was removed, 100 µl of 0.01N HCl was added and then incubated for 20 minutes at room temperature. Cell lysate (75 µl) along with 25 µl of assay buffer (supplied in FlashPlate™ cAMP assay kit available from NEN Life Science Products Boston, MA) into a Flashplate. cAMP standards and cAMP tracer were added following the kit's protocol. The flashplate was then incubated for 18 hours at 4 °C. The content of the wells were aspirated and counted in a Scintillation counter.

In Vivo Biological Assays

Cannabinoid agoinists such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and CP-55940 have been shown to affect four characteristic behaviors in mice, collectively known as the Tetrad. For a description of these behaviors see: Smith, P.B., et al. in "The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice." J. Pharmacol. Exp. Ther., **270**(1), 219-227 (1994) and Wiley, J., et al. in "Discriminative stimulus effects of anandamide in rats," Eur. J. Pharmacol., **276**(1-2), 49-54 (1995). Reversal of these activities in the Locomotor Activity, Catalepsy, Hypothermia, and Hot Plate assays described below provides a screen for *in vivo* activity of CB-1 antagonists.

All data is presented as % reversal from agonist alone using the following formula: (CP/agonist - vehicle/agonist)/(vehicle/vehicle - vehicle/agonist). Negative numbers indicate a potentiation of the agonist activity or non-antagonist activity. Positive numbers indicate a reversal of activity for that particular test.

Locomotor Activity

Male ICR mice (n=6) (17-19 g, Charles River Laboratories, Inc., Wilmington, MA) were pre-treated with test compound (sc, po, ip, or icv). Fifteen minutes later, the mice were challenged with CP-55940 (sc). Twenty-five minutes after the agonist injection, the mice were placed in clear acrylic cages (431.8 cm x 20.9 cm x 20.3 cm) containing clean wood shavings. The subjects were allowed to explore surroundings for a total of about 5 minutes and the activity was recorded by infrared motion detectors (available from Coulbourn Instruments™, Allentown, PA) that were placed on top of the cages. The data was computer collected and expressed as "movement units."

Catalepsy

Male ICR mice (n=6)(17-19 g upon arrival) were pre-treated with test compound (sc, po, ip or icv). Fifteen minutes later, the mice were challenged with CP-55940 (sc). Ninety minutes post injection, the mice were placed on a 6.5 cm steel ring attached to a ring stand at a height of about 12 inches. The ring was mounted in a horizontal orientation and the mouse was suspended in the gap of the ring with fore- and hind-paws gripping the perimeter. The duration that the mouse remained completely motionless (except for respiratory movements) was recorded over a 3-minute period.

The data were presented as a percent immobility rating. The rating was calculated by dividing the number of seconds the mouse remains motionless by the total time of the observation period and multiplying the result by 100. A percent reversal from the agonist was then calculated.

Hypothermia

Male ICR mice (n=5) (17-19 g upon arrival) were pretreated with test compounds (sc, po, ip or icv). Fifteen minutes later, mice were challenged with the cannabinoid agonist CP-55940 (sc). Sixty-five minutes post agonist injection, rectal body temperatures were taken. This was done by inserting a small thermostat probe approximately 2- 2.5 cm into the rectum. Temperatures were recorded to the nearest tenth of a degree

Hot Plate

Male ICR mice (n=7) (17-19 g upon arrival) are pre-treated with test compounds (sc, po, ip or iv). Fifteen minutes later, mice were challenged with a cannabinoid agonist CP-55940 (sc). Forty-five minutes later, each mouse was tested for reversal of analgesia using a standard hot plate meter (Columbus Instruments). The hot plate was 10" x 10" x 0.75" with a surrounding clear acrylic wall. Latency to kick, lick or flick hindpaw or jump from the platform was recorded to the nearest tenth of a second. The timer was experimenter activated and each test had a 40 second cut off. Data were presented as a percent reversal of the agonist induced analgesia.

Food Intake

The following screen was used to evaluate the efficacy of test compounds for inhibiting food intake in Sprague-Dawley rats after an overnight fast.

Male Sprague-Dawley rats were obtained from Charles River Laboratories, Inc. (Wilmington, MA). The rats were individually housed and fed powdered chow. They were maintained on a 12 hour light/dark cycle and received food and water *ad libitum*. The animals were acclimated to the vivarium for a period of one week before testing was conducted. Testing was completed during the light portion of the cycle.

To conduct the food intake efficacy screen, rats were transferred to individual test cages without food the afternoon prior to testing, and the rats were fasted overnight. After the

overnight fast, rats were dosed the following morning with vehicle or test compounds. A known antagonist was dosed (3 mg/kg) as a positive control, and a control group received vehicle alone (no compound). The test compounds were dosed at ranges between 0.1 and 100 mg/kg depending upon the compound. The standard vehicle was 0.5% (w/v) methylcellulose in water and the standard route of administration was oral. However, different vehicles and routes of administration were used to accommodate various compounds when required. Food was provided to the rats 30 minutes after dosing and the Oxymax automated food intake system (Columbus Instruments, Columbus, Ohio) was started. Individual rat food intake was recorded continuously at 10-minute intervals for a period of two hours. When required, food intake was recorded manually using an electronic scale; food was weighed every 30 minutes after food was provided up to four hours after food was provided. Compound efficacy was determined by comparing the food intake pattern of compound-treated rats to vehicle and the standard positive control.

Alcohol Intake

The following protocol evaluates the effects of alcohol intake in alcohol preferring (P) female rats (bred at Indiana University) with an extensive drinking history. The following references provide detailed descriptions of P rats: Li ,T.-K., et al., "Indiana selection studies on alcohol related behaviors" in Development of Animal Models as Pharmacogenetic Tools (eds McClearn C. E., Deitrich R. A. and Erwin V. G.), Research Monograph 6, 171-192 (1981) NIAAA, ADAMHA, Rockville, MD; Lumeng, L, et al., "New strains of rats with alcohol preference and nonpreference" Alcohol And Aldehyde Metabolizing Systems, 3, Academic Press, New York, 537-544 (1977); and Lumeng, L, et al., "Different sensitivities to ethanol in alcohol-preferring and -nonpreferring rats," Pharmacol, Biochem Behav., 16, 125-130 (1982).

Female rats were given 2 hours of access to alcohol (10% v/v and water, 2-bottle choice) daily at the onset of the dark cycle. The rats were maintained on a reverse cycle to facilitate experimenter interactions. The animals were initially assigned to four groups equated for alcohol intakes: Group 1 - vehicle (n =8); Group 2 –positive control (e.g. 5.6 mg/kg AM251; n = 8); Group 3 – low dose test compound (n = 8); and Group 4 – high dose of test compound (n = 8). Test compounds were generally mixed into a vehicle of 30% (w/v) β-cyclodextrin in distilled water at a volume of 1-2 ml/kg. Vehicle injections were given to all groups for the first two days of the experiment. This was followed by 2 days of drug injections (to the appropriate groups) and a final day of vehicle injections. On the drug injection days, drugs were given sc 30 minutes prior to a 2-hour alcohol access period. Alcohol intake for all animals was measured during the test period and a comparison was made between drug and vehicle-treated animals to determine effects of the compounds on alcohol drinking behavior.

Additional drinking studies were done utilizing female C57Bl/6 mice (Charles River). Several studies have shown that this strain of mice will readily consume alcohol with little to

no manipulation required (Middaugh et al., "Ethanol Consumption by C57BL/6 Mice: Influence of Gender and Procedural Variables" Alcohol, 17 (3), 175-183, 1999; Le et al., "Alcohol Consumption by C57BL/6, BALA/c, and DBA/2 Mice in a Limited Access Paradigm" Pharmacology Biochemisrty and Behavior, 47, 375-378, 1994).

For our purposes, upon arrival (17-19 g) mice were individually housed and given unlimited access to powdered rat chow, water and a 10 % (w/v) alcohol solution. After 2-3 weeks of unlimited access, water was restricted for 20 hours and alcohol was restricted to only 2 hours access daily. This was done in a manner that the access period was the last 2 hours of the dark part of the light cycle.

Once drinking behavior stabilized, testing commenced. Mice were considered stable when the average alcohol consumption for 3 days was ± 20% of the average for all 3 days. Day 1 of test consisted of all mice receiving vehicle injection (sc or ip). Thirty to 120 minutes post injection access was given to alcohol and water. Alcohol consumption for that day was calculated (g/kg) and groups were assigned (n=7-10) so that all groups had equivocal alcohol intake. On day 2 and 3, mice were injected with vehicle or test compound and the same protocol as the previous day was followed. Day 4 was wash out and no injections were given. Data was analyzed using repeated measures ANOVA. Change in water or alcohol consumption was compared back to vehicle for each day of the test. Positive results would be interpreted as a compound that was able to significantly reduce alcohol consumption while having no effect on water

Oxygen Consumption

Methods:

Whole body oxygen consumption is measured using an indirect calorimeter (Oxymax from Columbus Instruments, Columbus, OH) in male Sprague Dawley rats (if another rat strain or female rats are used, it will be specified). Rats (300-380g body weight) are placed in the calorimeter chambers and the chambers are placed in activity monitors. These studies are done during the light cycle. Prior to the measurement of oxygen consumption, the rats are fed standard chow ad libitum. During the measurement of oxygen consumption, food is not available. Basal pre-dose oxygen consumption and ambulatory activity are measured every 10 minutes for 2.5 to 3 hours. At the end of the basal pre-dosing period, the chambers are opened and the animals are administered a single dose of compound (the usual dose range is 0.001 to 10 mg/kg) by oral gavage (or other route of administration as specified, i.e. s.c., i.p., i.v.). Drugs are prepared in methylcellulose, water or other specified vehicle (examples include PEG400, 30% beta-cyclodextran and propylene glycol). Oxygen consumption and ambulatory activity are measured every 10 minutes for an additional 1-6 hours post-dosing.

The Oxymax calorimeter software calculates the oxygen consumption (ml/kg/h) based on the flow rate of air through the chambers and difference in oxygen content at inlet

and output ports. The activity monitors have 15 infrared light beams spaced one inch apart on each axis, ambulatory activity is recorded when two consecutive beams are broken and the results are recorded as counts.

Resting oxygen consumption, during pre- and post-dosing, is calculated by averaging the 10-min O_2 consumption values, excluding periods of high ambulatory activity (ambulatory activity count > 100) and excluding the first 5 values of the pre-dose period and the first value from the post-dose period. Change in oxygen consumption is reported as percent and is calculated by dividing the post-dosing resting oxygen consumption by the pre-dose oxygen consumption *100. Experiments will typically be done with n = 4-6 rats and results reported are mean +/- SEM.

Interpretation:

An increase in oxygen consumption of >10% is considered a positive result. Historically, vehicle-treated rats have no change in oxygen consumption from pre-dose basal.

Administration of the compositions of this invention can be via any method which delivers a compound of this invention systemically and/or locally. These methods which include oral routes and transdermal routes, etc. Generally, the compounds of this invention are administered orally, but parenteral administration may be utilized (e.g., intravenous, intramuscular, subcutaneous or intramedullary). The two different compounds of this invention can be co-administered simultaneously or sequentially in any order, or single pharmaceutical composition comprising a NRPA as described above and a CB-1 receptor antagonist as described above in a pharmaceutically acceptable carrier can be administered.

The amount and timing of compounds administered will, of course, be based on the judgment of the prescribing physician. Thus, because of patient to patient variability, the dosages given below are a guideline and the physician may titrate doses of the agent to achieve the activity that the physician considers appropriate for the individual patient. In considering the degree of activity desired, the physician must balance a variety of factors such as cognitive function, age of the patient, presence of preexisting disease, as well as presence of other diseases (e.g., cardiovascular). The following paragraphs provide preferred dosage ranges for the various components of this invention (based on average human weight of 70 kg).

In general, an effective dosage for the NRPA in the range of 0.001 to 200 mg/kg/day, preferably 0.005 to 10.0 mg/kg/day.

In general, an effective dosage for the CB-1 receptor agonist, when used in the combination compositions and methods of this invention, is in the range of 0.001 to 200 mg/kg/day, preferably 0.05 to 10.0 mg/kg/day.

The compositions of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable vehicle or diluent. Thus, the compounds of this invention

can be administered individually or together in any conventional oral, parenteral or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipient such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g.,topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, are prepared.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Pharmaceutical compositions according to the invention may contain 0.1 - 95% of the compound(s) of this invention, preferably 1 - 70%. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the obesity or compulsive overeating of the subject being treated.

Claims

1. A pharmaceutical composition for the treatment of obesity, compulsive overeating, or to promote or facilitate weight loss comprising:

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof;

(b) a CB-1 receptor antagonist or pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier;

wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating obesity, compulsive overeating or promoting or facilitating weight loss.

2. The pharmaceutical composition according to Claim 1, wherein said CB-1 receptor antagonist is selected from: 1-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-ethylamino-azetidine-3-carboxylic acid amide; 1-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-ethylamino-azetidine-3-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 1-{1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-phenylpiperidin-4-yl}-ethanone; {3-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-3-(1α,5α,6α)-azabicyclo[3.1.0]hex-6-yl}-dimethylamine; 6-(1-benzylpyrrolidin-3-yloxy)-9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purine; 9-(4-chlorophenyl)-6-(1-cyclohexylazetidin-3-yloxy)-8-(2,4-dichlorophenyl)-9H-purine; 6-tert-butoxy-9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purine; 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-isopropoxy-9H-purine; 1-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-propylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-2-methyl-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-pyrrolidin-1-yl-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 8-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 9-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-methyl-4-oxa-1,9-diazaspiro[5.5]undecan-2-one; 8-[9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-phenylpiperidin-4-ol; 4-benzyl-1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidin-4-ol; 4-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperazine-2-carboxylic acid methylamide; 9-(4-chlorophenyl)-8-(2,4-

dichlorophenyl)-6-(4-pyridin-2-yl-piperazin-1-yl)-9H-purine; and 9-(4-chlorophenyl)-8-(2,4-dichlorophenyl)-6-(4-pyrimidin-2-yl-piperazin-1-yl)-9H-purine; 1-[9-(4-chlorophenyl)-8-(2-fluorophenyl)-9H-purin-6-yl]-4-isopropylamino-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-isopropylamino-piperidine-4-carboxylic acid amide; 4-amino-1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidine-4-carboxylic acid amide; 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylamino-piperidine-4-carboxylic acid amide; 8-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 4-amino-1-[9-(4-chloro-phenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-piperidine-4-carboxylic acid amide; and 1-[9-(4-chlorophenyl)-8-(2-chlorophenyl)-9H-purin-6-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

3. The pharmaceutical composition according to claim 1, wherein the CB-1 receptor antagonist is selected from: 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-methylpiperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-(4-pyrimidin-2-ylpiperazin-1-yl)-pyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-[(1S,4S)-5-methanesulfonyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-2-methylpyrazolo[1,5-a][1,3,5]triazine; and 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-[4-(propane-2-sulfonyl)-piperazin-1-yl]-pyrazolo[1,5-a][1,3,5]triazine; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-methylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-fluorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 3-amino-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-azetidine-3-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-methylaminoazetidine-3-carboxylic acid amide; and 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-dimethylaminoazetidine-3-carboxylic acid amide; 1-{1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-phenylpiperidin-4-yl}-ethanone; 3-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-azabicyclo[3.1.0]hex-6-ylamine; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 4-benzyl-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-

a][1,3,5]triazin-4-yl]-piperidin-4-ol; 2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-5-methyl-2,5,7-triazaspiro[3.4]octan-8-one; 2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-2,5,7-triazaspiro[3.4]octan-8-one; 8-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 2-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-6,6-dimethyl-2,5,7-triazaspiro[3.4]octan-8-one; 4-(1-benzylpyrrolidin-3-yloxy)-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-(1-cyclohexylazetidin-3-yloxy)-2-methylpyrazolo[1,5-a][1,3,5]triazine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-4-isopropoxy-2-methylpyrazolo[1,5-a][1,3,5]triazine; and 4-tert-butoxy-7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazine; butyl-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-amine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-piperidin-1-yl-pyrazolo[1,5-a][1,3,5]triazine; [7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-[2-(4-fluorophenyl)-ethyl]-amine; 7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methyl-4-morpholin-4-yl-pyrazolo[1,5-a][1,3,5]triazine; and [7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-(2-morpholin-4-yl-ethyl)-amine; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 3-amino-1-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-azetidine-3-carboxylic acid amide; and 8-[7-(2-chlorophenyl)-8-(4-chlorophenyl)-2-methylpyrazolo[1,5-a][1,3,5]triazin-4-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

4. The pharmaceutical composition according to claim 1, wherein said CB-1 receptor antagonist is selected from: 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-(4-methyl-piperazin-1-yl)-pyrazolo[1,5-a]pyrimidine; 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-(4-pyrimidin-2-yl-piperazin-1-yl)-pyrazolo[1,5-a]pyrimidine; 3-(4-chloro-phenyl)-2-(2-chlorophenyl)-7-[(1S,4S)-5-methanesulfonyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-pyrazolo[1,5-a]pyrimidine; and 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-[4-(propane-2-sulfonyl)-piperazin-1-yl]-pyrazolo[1,5-a]pyrimidine; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 3-amino-1-[3-(4-chlorophenyl)-2-(2-

chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-azetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-6-methylpyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-isopropylaminoazetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-5,6-dimethylpyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylamino-azetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-methylaminoazetidine-3-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; 1-{1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-phenylpiperidin-4-yl}-ethanone; 3-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-(1a,5a,6a)-azabicyclo[3.1.0]hex-6-ylamine; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-(4-fluorophenyl)-piperidin-4-ol; 4-benzyl-1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-piperidin-4-ol; 8-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 2-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-2,5,7-triazaspiro[3.4]octan-8-one; 8-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-6-methylpyrazolo[1,5-a]pyrimidin-7-yl]-1-isopropyl-1,3,8-triazaspiro[4.5]decan-4-one; 2-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-5-methyl-2,5,7-triazaspiro[3.4]octan-8-one; 7-(1-benzylpyrrolidin-3-yloxy)-3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidine; and 3-(4-chlorophenyl)-2-(2-chlorophenyl)-7-(1-cyclohexylazetidin-3-yloxy)-pyrazolo[1,5-a]pyrimidine; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-ethylaminopiperidine-4-carboxylic acid amide; 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-4-isopropylaminopiperidine-4-carboxylic acid amide; and 1-[3-(4-chlorophenyl)-2-(2-chlorophenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-3-ethylaminoazetidine-3-carboxylic acid amide; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of said compound or said salt.

5. The pharmaceutical composition according to claim 1, wherein said CB-1 receptor antagonist is selected from: 5-(4-chloro-phenyl)-3-(5-cyclohexyl-1H-imidazol-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole; 5-(4-chloro-phenyl)-3-(2-cyclohexyl-3H-imidazol-4-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-3-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-3-[1-(1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-3-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; 5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-3-[1-(2,2-dimethyl-tetrahydro-pyran-4-yl)-1H-imidazol-4-yl]-4-methyl-1H-pyrazole: 5-{2-(2,4-dichloro-phenyl)-4-methyl-5-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-2H-pyrazol-3-yl}-2-methoxy-pyridine; and 1-(2-

chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-3-[1-(1-methyl-1-phenyl-ethyl)-1H-imidazol-4-yl]-1H-pyrazole; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of the compound or the salt.

6. The pharmaceutical composition according to claim 1, wherein said CB-1 receptor antagonist is selected from: 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-1H-pyrrole-2-carbonyl)-piperazin-1-yl]-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[4-(1-methyl-cyclopropanecarbonyl)-piperazin-1-yl]-ethanone; N-(1-{2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-oxo-ethyl}-piperidin-4-yl)-2,2,2-trifluoro-acetamide; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanone; 1-[5-(4-chloro-phenyl)-1-(2-fluoro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(4-trifluoroacetyl-piperazin-1-yl)-ethanone; 1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-pyrrolidin-1-yl-ethanone; 1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-[1,4]oxazepan-4-yl-ethanone; and 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(1-oxa-8-aza-spiro[4.5]dec-8-yl)-ethanone; and a pharmaceutically acceptable salt thereof, or a solvate or hydrate of the compound or the salt.

7. The pharmaceutical composition according claim 1, wherein said CB-1 receptor antagonist is selected from: 2-(benzyl-isopropyl-amino)-1-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-ethanol; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,5-dimethyl-piperidin-1-yl)-ethanol; 1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-hydroxy-ethyl}-4-isopropylamino-piperidine-4-carboxylic acid amide; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-(3,3-dimethyl-piperidin-1-yl)-ethanol; 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-piperidin-1-yl-ethanol; and 1-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-2-morpholin-4-yl-ethanol; and a pharmaceutically acceptable salt thereof, or hydrate of the compound or the salt.

8. The pharmaceutical composition according to claim 1 wherein said CB-1 receptor antagonist is selected from: 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-cyclohexyl-morpholine; 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(propane-2-sulfonyl)-morpholine; 2-[5-(4-chloro-phenyl)-1-(2-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(toluene-4-sulfonyl)-morpholine; 1-{2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-morpholin-4-yl}-2-methyl-propan-1-one; and 2-[1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-4-(4-trifluoromethyl-

benzyl)-morpholine; and a pharmaceutically acceptable salt thereof or a solvate or hydrate of the compound or the salt.

9. The pharmaceutical composition according claim 1, wherein said CB-1 receptor antagonist is selected from: 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-piperidin-1-yl-ethanone and 1-[1-(4-chloro-phenyl)-2-(2,4-dichloro-phenyl)-5-methyl-1H-imidazol-4-yl]-2-morpholin-4-yl-ethanone; and a pharmaceutically acceptable salt thereof, a or a solvate or hydrate of the compound, or the salt.

10. The pharmaceutically composition according to Claim 1, wherein said nicotinic receptor partial agonist is selected from:

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-ethyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-vinyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-bromo-3-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
3-benzyl-9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;
9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-ethynyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-propyl)- 1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;
9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(4-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(3-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(3,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,4-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,5-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

6-methyl-5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

5-oxo-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

6-oxo-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

4,5-difluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

4-ethynyl-5-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

5-ethynyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene-4-carbonitrile;

6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-methyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

7-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6-methyl-7-phenyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

14-methyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

4-chloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;

1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-ol;

7-methyl-5-oxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2,4(8),6,9-tetraene;

4,5-dichloro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;

1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;

4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5,6-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

5-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

6-(trifluoromethyl)-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

7-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

6-methyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

6,7-dimethyl-5,8,15-triazatetracyclo[11.3.1.$0^{2,11}$.$0^{4,9}$]heptadeca-2(11),3,5,7,9-pentaene;

7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

5-methyl-7-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

7-methyl-5-oxa-6,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

4,5-difluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

4-chloro-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-chloro-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

4-(1-ethynyl)-5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-(1-ethynyl)-4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-6-ol;

6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol;

4-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-nitro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

5-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

6-hydroxy-5-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene; and

their pharmaceutically acceptable salts and their optical isomers.

11. The pharmaceutical composition according to Claim 10 wherein said nicotinic receptor partial agonist is selected from:

9-bromo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-chloro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-fluoro-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-a][1,5]diazocin-8-one;

9-acetyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-iodo-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-cyano-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-carbomethoxy-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-carboxyaldehyde-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2,6-difluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

9-(2-fluorophenyl)-1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2a][1,5]diazocin-8-one;

6-methyl-5-thia-5-dioxa-6,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,8-triene;

4-fluoro-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-trifluoromethyl-10-aza-tricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

4-nitro-10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-triene;

6-methyl-5,7,13-triazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]hexadeca-2(11),3,5,7,9-pentaene;

5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

6-methyl-5-oxa-7,13-diazatetracyclo[9.3.1.$0^{2,10}$.$0^{4,8}$]pentadeca-2(10),3,6,8-tetraene;

10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl cyanide;

1-(10-azatricyclo[6.3.1.$0^{2,7}$]dodeca-2(7),3,5-trien-4-yl)-1-ethanone;

11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-ethanone;

1-[11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-yl]-1-propanone;

4-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-5-carbonitrile;

5-fluoro-11-azatricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene-4-carbonitrile;

6-methyl-7-thia-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6,7-dimethyl-5,7,14-triazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-7-oxa-5,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,5,8-tetraene;

6-methyl-5-oxa-7,14-diazatetracyclo[10.3.1.$0^{2,10}$.$0^{4,8}$]hexadeca-2(10),3,6,8-tetraene;

5,6-difluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-trifluoromethyl-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene;

6-methoxy-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

6-fluoro-11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-triene;

11-aza-tricyclo[7.3.1.$0^{2,7}$]trideca-2(7),3,5-trien-5-ol, and their pharmaceutically acceptable salts and their optical isomers thereof.

12. A method of treating obesity, overeating, and/or facilitating or promoting weight loss in a mammal comprising administering to said mammal respectively an anti-obesity attenuating effective amount of a pharmaceutical composition comprising

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof; and

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof;

wherein the active ingredients (a) and (b) are present in amounts that render the composition effective in the treatment of obesity, compulsive overeating or an overweight condition.

13. The method according to claim 12, wherein the nicotinic receptor partial agonist and the CB-1 receptor antagonist are administered substantially simultaneously.

14. A pharmaceutical composition according to claim 1 for treating a disorder or condition selected from the group consisting of disorders and conditions in which obesity or an overweight condition predominates, including Type 2 diabetes mellitus, hypertension, dyslipidemia and increased mortality in a mammal, the method comprising:

(a) a nicotinic receptor partial agonist or a pharmaceutically acceptable salt thereof;

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier;

wherein the active agents "a" and "b" above are present in amounts that render the composition effective in treating such disorder or condition.

15. A method of treating a disorder or condition according to claim 12 selected from the groups of disorders and conditions in which obesity or an overweight condition predominates in a mammal including Type 2 diabetes mellitus, hypertension, dyslipidemia and increased morality, the method comprising administering to said mammal:

(a) a nicotinic receptor partial agonist ar a pharmaceutically acceptable salt thereof; and

(b) a CB-1 receptor antagonist or a pharmaceutically acceptable salt thereof;

wherein the active agent "a" and "b" above are present in amounts that render the composition effective that render the composition effective in treating such disorder or condition.

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(54) Title: A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF OBESITY OR TO FACILITATE OR PROMOTE WEIGHT LOSS

(57) Abstract: Pharmaceutical compositions are disclosed for the treatment of obesity, an overweight condition and compulsive overeating. The pharmaceutical compositions are comprised of a therapeutically effective combination of a nicotinic receptor partial agonist and a CB-1 receptor antagonist and a pharmaceutically acceptable carrier. The method of using these compounds is also disclosed.

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 159 970 A (PFIZER PROD INC) 5 December 2001 (2001-12-05) the whole document	1-15
Y	WO 98/18798 A (PFIZER ; NEILL BRIAN THOMAS O (US)) 7 May 1998 (1998-05-07) cited in the application claims 1-30	1-15
Y	WO 99/35131 A (PFIZER PROD INC ; BROOKS PAIGE ROANNE PALMER (US); COE JOTHAM WADSWORT) 15 July 1999 (1999-07-15) cited in the application page 6; claims 1-14	1-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Blott, C

INTERNATIONAL SEARCH REPORT

onal Application No
IB2004/001415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/55680 A (PFIZER PROD INC ; COE JOTHAM WADSWORTH (US)) 4 November 1999 (1999-11-04) cited in the application pages 5-7; claims 1-11	1-15
X	WO 01/58450 A (SANOFI SYNTHELABO ; MENARD FRANCOIS (FR); BLANCHARD JEAN CHARLES (FR)) 16 August 2001 (2001-08-16) page 1, lines 1-26; claim 7	1-11,14
Y	WO 03/027076 A (SOLVAY PHARM BV ; HERREMANS ARNOLDUS H J (NL); KRUSE CORNELIS G (NL);) 3 April 2003 (2003-04-03) page 4, lines 25-32; claims 1-3,9,10	1-15
Y	WO 02/28346 A (AVENTIS PHARMA SA ; PIOT GROSJEAN ODILE (FR); PICAUT PHILIPPE (FR); PE) 11 April 2002 (2002-04-11) page 1, lines 1-11; claims 1-12	1-15
Y	WO 01/64634 A (AVENTIS PHARMA SA) 7 September 2001 (2001-09-07) page 26, lines 4,24	1-15
Y	WO 98/32441 A (SANOFI SA ; MARUANI JEANNE (FR); SOUBRIE PHILIPPE (FR)) 30 July 1998 (1998-07-30) claims 1,5	1-15
Y	WO 01/32663 A (SANOFI SYNTHELABO ; BARTH FRANCIS (FR); CONGY CHRISTIAN (FR); MARTINEZ) 10 May 2001 (2001-05-10) page 1, lines 1-8; claims 1,16	1-15
E	WO 2004/037823 A (GRIFFITH DAVID ANDREW ; PFIZER PROD INC (US)) 6 May 2004 (2004-05-06) page 1, lines 1-12; claim 9; examples 1-32 page 50, line 5 page 53, line 8	1,2,14
E	WO 2004/069837 A (GRIFFITH DAVID ANDREW ; PFIZER PROD INC (US)) 19 August 2004 (2004-08-19) page 1, lines 1-10; examples 1-14 page 55, line 2 page 58, line 8	1,3,14

-/--

INTERNATIONAL SEARCH REPORT

onal Application No
IB2004/001415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2004/069838 A (GRIFFITH DAVID ANDREW ; PFIZER PROD INC (US)) 19 August 2004 (2004-08-19) page 1, lines 1-10; examples 1-17 page 27, line 25 page 28, line 15	1,4,14
E	WO 2004/035566 A (DOW ROBERT LEE ; PFIZER PROD INC (US)) 29 April 2004 (2004-04-29) page 1, lines 1-10; claims 12,13; tables 1a,1b	1,5,14
E	WO 2004/052864 A (DOW ROBERT LEE ; HAMMOND MARLYS (US); PFIZER PROD INC (US)) 24 June 2004 (2004-06-24) page 1, lines 1-12; claims 7,9,11; tables 1-5	1,6-9,14

INTERNATIONAL SEARCH REPORT

Information on patent family members

ional Application No
IB2004/001415

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1159970 A	05-12-2001	BR 0102211 A	05-03-2002
		CA 2349388 A1	02-12-2001
		EP 1159970 A2	05-12-2001
		JP 2002012558 A	15-01-2002
		US 2003176457 A1	18-09-2003
		US 2002010192 A1	24-01-2002
WO 9818798 A	07-05-1998	AU 4394897 A	22-05-1998
		EP 0937077 A1	25-08-1999
		HR 970567 A1	31-10-1998
		WO 9818798 A1	07-05-1998
		ID 18741 A	07-05-1998
		JP 2000505809 T	16-05-2000
		US 6235734 B1	22-05-2001
		US 2003065173 A1	03-04-2003
		ZA 9709706 A	29-04-1999
WO 9935131 A	15-07-1999	AP 1170 A	30-06-2003
		AU 753389 B2	17-10-2002
		AU 9641698 A	26-07-1999
		BG 104561 A	31-01-2001
		BR 9814592 A	17-10-2000
		CA 2316921 A1	15-07-1999
		CN 1285821 T	28-02-2001
		CZ 20002438 A3	13-11-2002
		EA 3190 B1	27-02-2003
		EP 1044189 A1	18-10-2000
		HR 20000445 A1	30-04-2001
		HU 0100949 A2	28-08-2001
		WO 9935131 A1	15-07-1999
		JP 3550359 B2	04-08-2004
		JP 2002500218 T	08-01-2002
		NO 20003422 A	29-08-2000
		NZ 504482 A	31-01-2003
		OA 11428 A	03-05-2004
		PL 341824 A1	07-05-2001
		SG 102686 A1	26-03-2004
		SK 9712000 A3	05-03-2002
		TR 200001840 T2	21-12-2000
		TW 513412 B	11-12-2002
		US 2002072524 A1	13-06-2002
		US 2002072525 A1	13-06-2002
		US 2002111350 A1	15-08-2002
		US 2002132824 A1	19-09-2002
		US 2003130261 A1	10-07-2003
		US 2003130260 A1	10-07-2003
		US 6410550 B1	25-06-2002
		US 6605610 B1	12-08-2003
		ZA 9811911 A	29-06-2000
WO 9955680 A	04-11-1999	AP 1154 A	27-03-2003
		AT 258921 T	15-02-2004
		AU 749831 B2	04-07-2002
		AU 2951699 A	16-11-1999
		BG 104983 A	28-09-2001
		BR 9910058 A	26-12-2000
		CA 2330576 A1	04-11-1999
		CN 1144787 T	07-04-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

ional Application No
IB2004/001415

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9955680 A		DE	69914594 D1	11-03-2004
		DK	1076650 T3	24-05-2004
		EA	3669 B1	28-08-2003
		EP	1076650 A1	21-02-2001
		ES	2213354 T3	16-08-2004
		HR	20000731 A1	30-06-2001
		HU	0103340 A2	28-02-2002
		WO	9955680 A1	04-11-1999
		ID	26700 A	01-02-2001
		JP	2002513007 T	08-05-2002
		NO	20005397 A	26-10-2000
		NZ	507035 A	30-05-2003
		OA	11506 A	14-05-2004
		PL	344010 A1	24-09-2001
		SI	1076650 T1	30-06-2004
		SK	15952000 A3	04-06-2002
		TR	200003122 T2	21-03-2001
		US	2003008890 A1	09-01-2003
		US	6462035 B1	08-10-2002
		US	2004167149 A1	26-08-2004
		ZA	9902971 A	30-10-2000
WO 0158450 A	16-08-2001	FR	2804604 A1	10-08-2001
		AU	3562001 A	20-08-2001
		BG	106946 A	30-05-2003
		BR	0108126 A	28-01-2003
		CA	2397262 A1	16-08-2001
		CN	1406128 T	26-03-2003
		CZ	20022698 A3	13-11-2002
		EE	200200439 A	15-12-2003
		EP	1257275 A2	20-11-2002
		WO	0158450 A2	16-08-2001
		HU	0300237 A2	28-07-2003
		JP	2003522145 T	22-07-2003
		NO	20023765 A	09-10-2002
		PL	358221 A1	09-08-2004
		SK	11292002 A3	04-02-2003
		US	2003087933 A1	08-05-2003
		ZA	200205317 A	04-09-2003
WO 03027076 A	03-04-2003	BR	0212481 A	24-08-2004
		CA	2457444 A1	03-04-2003
		WO	03027076 A2	03-04-2003
		EP	1438296 A2	21-07-2004
		HR	20040185 A2	31-08-2004
		US	2004235854 A1	25-11-2004
WO 0228346 A	11-04-2002	FR	2814678 A1	05-04-2002
		AT	267595 T	15-06-2004
		AU	9393601 A	15-04-2002
		BG	107739 A	30-01-2004
		BR	0114410 A	17-02-2004
		CA	2424934 A1	11-04-2002
		CN	1473040 T	04-02-2004
		DE	60103556 D1	01-07-2004
		DK	1328269 T3	20-09-2004
		EP	1328269 A2	23-07-2003
		ES	2217191 T3	01-11-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
IB2004/001415

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0228346 A		WO 0228346 A2	11-04-2002
		HU 0302044 A2	28-11-2003
		JP 2004512279 T	22-04-2004
		NO 20031521 A	24-04-2003
		PT 1328269 T	31-08-2004
		SI 1328269 T1	31-10-2004
		SK 4032003 A3	11-09-2003
		TR 200401264 T4	21-07-2004
		US 2002091114 A1	11-07-2002
		ZA 200303015 A	26-02-2004
WO 0164634 A	07-09-2001	FR 2805817 A1	07-09-2001
		AU 3752701 A	12-09-2001
		BG 107058 A	31-07-2003
		BR 0108893 A	05-11-2002
		CA 2400141 A1	07-09-2001
		CN 1418192 T	14-05-2003
		EE 200200485 A	16-02-2004
		EP 1263722 A1	11-12-2002
		WO 0164634 A1	07-09-2001
		HU 0400636 A2	28-06-2004
		JP 2003525270 T	26-08-2003
		MX PA02008349 A	13-12-2002
		NO 20024177 A	29-10-2002
		NZ 521077 A	24-09-2004
		SK 12432002 A3	03-06-2003
		US 6355631 B1	12-03-2002
		ZA 200206912 A	03-11-2003
WO 9832441 A	30-07-1998	FR 2758723 A1	31-07-1998
		AU 6219398 A	18-08-1998
		BR 9806801 A	16-05-2000
		CA 2278661 A1	30-07-1998
		EE 9900304 A	15-02-2000
		EP 0969835 A1	12-01-2000
		WO 9832441 A1	30-07-1998
		HR 980042 A1	31-10-1998
		ID 22216 A	16-09-1999
		JP 2001501971 T	13-02-2001
		LV 12354 A ,B	20-10-1999
		NO 993634 A	27-09-1999
		SK 99799 A3	12-06-2000
		TR 9901721 T2	21-10-1999
		TW 450808 B	21-08-2001
		US 2002128302 A1	12-09-2002
		US 6344474 B1	05-02-2002
		ZA 9800691 A	05-08-1998
WO 0132663 A	10-05-2001	FR 2800375 A1	04-05-2001
		AU 1286001 A	14-05-2001
		EP 1230244 A2	14-08-2002
		WO 0132663 A2	10-05-2001
		HU 0203509 A2	28-03-2003
		JP 2003513099 T	08-04-2003
WO 2004037823 A	06-05-2004	WO 2004037823 A1	06-05-2004
		NL 1024643 A1	03-05-2004
		US 2004092520 A1	13-05-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
IB2004/001415

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004069837 A	19-08-2004	WO 2004069837 A1	19-08-2004
		NL 1025404 A1	09-08-2004
		US 2004157839 A1	12-08-2004
WO 2004069838 A	19-08-2004	WO 2004069838 A1	19-08-2004
		US 2004157838 A1	12-08-2004
WO 2004035566 A	29-04-2004	WO 2004035566 A1	29-04-2004
		US 2004077650 A1	22-04-2004
WO 2004052864 A	24-06-2004	WO 2004052864 A1	24-06-2004
		US 2004122074 A1	24-06-2004